pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment or derivative of the human neutral sphingomyelinase has at least about 50% of the activity of the protein of SEQ ID NO.2.

Please add the following new claim 31.

31. (New) The method of claim 13, wherein the fragment or derivative of the recombinant human neutral sphingomyelinase is at least about 70% identical to the protein of SEQ ID NO. 2.

REMARKS

Claim 13 has been amended. Support for the amendment can be found throughout the instant application including the Drawings and claims as filed originally. See eg., pg. 8, lines 16-23. New claim 31 finds particular support at pg. 9, lines 11-20. The amendment and new claim introduces no new matter to the application.

As an initial matter, the undersigned respectfully requests a telephone interview with PTO Examiners Rao and P.Achutamurthy (SPE) to discuss basis for the outstanding rejections, particularly the §103 rejection addressed below. Respectfully, it is believed that the §103 rejection is improper. The undersigned will call Examiner Rao to arrange a convenient time for the interview.

Turning to the Office Action, claims 13 and 15-17 stand rejected under 35 USC §112, second paragraph as being indefinite. Although Applicant respectfully disagrees with the rejection, basis for it has been addressed by this submission.

In particular, claim 13 has been amended to point out that intended derivatives of the human neutral sphingomyelinase have at least about 50% of the activity of the protein of SEQ ID NO.2. That activity can be readily quantified by enzymatic (N-SMAse) assays disclosed in the specification eg., at pg. 8, lines 16-23 and Examples 1 and 2.

Accordingly, reconsideration and withdrawal of the rejection are requested.

Claims 13 and 15-17 stand rejected under 35 USC §112, first paragraph, as not being enabling for derivatives of the recited human neutral sphingomyelinase. Applicant must respectfully disagree.

As understood, the PTO took the position that the claimed invention is not supported by the present disclosure because it would be too difficult to predict which amino acid changes can be tolerated by the enzyme and still obtain activity. See the Action at pg. 3. Respectfully, that position is without merit especially in view of Applicant's detailed specification. As that specification makes clear, practice of the invention is not limited to any particular N-Smase so long as it can provide acceptable function. See eg., pg. 15, lines 25-29 ; pg. 16, lines 4-15; and pg. 17, lines 8-10 (disclosing particular invention methods in which suitable enzyme fragments or derivatives are used).

Particular examples of acceptable N-Smases are disclosed throughout the present application. For example, pg. 7, lines 19-26 and Figures 1 and 2 disclose physical characteristics of the preferred native enzyme. Additionally suitable enzyme fragments or derivatives provide good activity in the standard activity gel assays as discussed eg., at pg. 8, lines 16-23. Preferred activity ranges in the assay have also been provided. Moreover, N-Smase fragments or derivatives with particular amino acid substitutions are disclosed at pg. 9, lines 1-20, for example. Nucleic acids that encode such suitable N-Smases are provided at pg. 10, lines 12-24. Nucleic acids having preferred basepair sizes and N-Smases having desired functional domains

are provided at pg. 10, line 12 to pg. 11, line 4. Suitable enzyme isoforms are taught at pg. 11, lines 21-25.

Thus contrary to the position of the USPTO, the instant specification provides a variety of suitable S-Nmases, fragments and derivatives with which to use the invention.

As understood, the rejection takes the position that notwithstanding Applicants' disclosure of many specific N-Smases suitable for use with the claimed invention, use of anything but the native enzyme (or fragments) is not enabled on grounds that it would require undue experimentation to make and use derivatives of the native N-Smase. That position cannot withstand scrutiny.

The specification provides examples of suitable N-Smases for use with the claimed invention including, but not limited to, the native enzyme. Should use of a particular enzyme fragment or derivative be needed in a specific invention embodiment, the specification provides more than ample guidance about selecting an appropriate fragment or derivative.

For example, preferred N-Smases including the native enzyme as well as fragments or derivatives thereof, exhibit good activity in the activity assay using ^{14}C-sphingomyelin and N-Smase peptide. See pg. 8, lines 16-23; and Example 6.

Moreover, the chemical structure of the native N-Smase has disclosed both at the amino acid and nucleic acid levels. See Figures 1 and 2, for example. Important function domains in the structure are recognized. See pgs. 10-11, for example. Methods for producing suitable N-Smases, preferably by use of conventional recombinant means have been disclosed. See pg. 11, line 27 to pg. 12, line 10.

Accordingly, it is believed that any testing needed to identify or confirm suitable N-Smases for use with the claimed invention, including appropriate fragments or derivatives, is

well within the level of experimentation permitted by the Federal Circuit. *In re Wands*, 8 USPQ2d 1400 (Fed. Cir. 1988).

Applicants disagree with the rejection on other grounds.

For example, a worker in this field would be able to use the guidance provided by the instant disclosure to select appropriate N-Smases including fragments or derivatives thereof. Any inoperable embodiments, to the extent they would exist at all, could be readily avoided.

Thus, one of skill having read Applicants' disclosure would know to identify suitable N-Smases including the native enzyme as well as fragments or derivatives thereof. Even if one assumes, *arguendo*, that a particular N-Smase fragment or derivative did not exhibit acceptable activity, that result, by itself, would not support the present enablement rejection. The worker would understand that another fragment or derivative as provided by the specification, could be tested and identified for suitable activity.

Applicant respectfully points out that the rejection has not provided any reason to doubt that the guidance provided by Applicants' disclosure could not be used to identify a range of acceptable N-Smase fragments or derivatives for use with the claimed methods.

In view of the guidance provided by the specification and the level of skill in this particular field, the claimed invention is amply supported by the application as filed originally. Further, practice of the claimed invention does not depend on knowing what changes or cannot be tolerated in the N-Smase protein. With particular respect to items A-D on pg. 4 of the Action, the requested information is simply not needed to make or use the invention as claimed.

Applicant disagrees with the rejection on another ground.

The claims have been rejected as obvious. It is not seen how the PTO can make that allegation, while at the same time, taking the position the invention is not enabled by the present

disclosure. On this basis alone, there is no grounds for the 35 USC §112, first paragraph, rejection.

Reconsideration and withdrawal of the rejection are respectfully requested.

Claims 13 and 15-17 stand rejected under 35 USC §112, second paragraph as containing subject matter which is not described in the specification. Applicant respectfully disagrees.

As discussed above, the instant specification describes a wide variety of acceptable enzymes (S-Nmases) including native enzyme as well as suitable fragments or derivatives thereof. The position that the application "discloses only a single species of the claimed genus...", as stated on pg. 5 is simply untrue. Many acceptable enzymes, fragments and derivatives have been described. See eg., Applicant's disclosure at pg. 7, lines 19-26; Figures 1 and 2; pg. 8, lines 16-23; pg. 9, lines 1-20; pg. 10, lines 12-24; pg. 10, line 12 to pg. 11, line 4; and pg. 11, lines 21-25.

Reconsideration and withdrawal of the rejection are requested.

Claims 13-17 stand rejected as being obvious under 35 USC §103 over Chatterjee et al. (JBC (1989) 264: 12554); Ogita et al. (WO 95/18119); and Ausubel et al. (Current Protocols in Molecular Biology). Applicants respectfully traverse the rejection.

As mentioned, the undersigned would like to discuss basis for this rejection with Examiners Rao and SPE Achutamurthy in a telephone interview.

To assist the Examiners, it is believed that a short statement of the invention and basis for the §103 rejection would be helpful.

The method of claim 13 features use of a recombinant human sphingomyelinase (N-Smase) to identify certain compounds. The Office rejected the claim as obvious in view of Chatterjee (disclosing isolation N-Smase protein from urine); Ogita (reporting sphingomyelinase inhibitor (F-10463a) and a preparation method); and Ausbel (a general molecular biology textbook). The Office has acknowledged that **Chatterjee and Ogita do not teach use of *recombinant* N-Smase** in the claimed method. See the Action at pg. 7. Nonetheless, the PTO contends that (Action at pg. 8):

> It would have been obvious to one of skill in the art at the time the invention was made to ***use the purified protein of Chatterjee et al. to obtain a cDNA clone and make recombinant sphingomyelinase using the techniques of Ausbel et al.*** and use it to develop a method of identifying other compounds which inhibit sphingomyelinase on line with Ogita et al.

The PTO has not pointed to anything in the cited references that shows how to make the cDNA clone captioned above. It merely relies on Ausubel for general information about how the cDNA might be made in view of the citations. As surprisingly, the Office assumes (without any support) that it would be obvious to make probes and use a cDNA library to obtain the cDNA. Action at pgs. 7-8, bridging paragraph. **No protein or nucleic acid sequence has been cited by the PTO** that would allow one to perform these steps, particularly the step of making a suitable probe(s). Accordingly, there is no basis for maintaining this rejection.

Indeed, it is an object of the invention to provide protein and nucleic acid sequence information that would allow a worker to make and use the recombinant enzyme of the claimed method. See the Summary of the Invention. That information is not disclosed by the cited references when taken together or alone. To allege that the information is obvious in view of those citations is technically without merit and is nothing more than hindsight reconstruction of the invention. That approach to examining patent applications has long been expressly disapproved by the Federal Circuit.

Respectfully, no *prima facie* case for obviousness has been made by the USPTO. Knowledge of general gene cloning methods, without more, is not sufficient to render a

particular DNA molecules obvious. See *In re Bell* 51 F.3d 1552 (Fed. Cir. 1995); and MPEP § 2144.09.

Furthermore, the Federal Circuit made it abundantly clear that prior art disclosure of a protein sequence does not necessarily render particular DNA molecules encoding the protein obvious. See eg., *In re Deuel*, 51 F.3d 1552, 1558-59, (Fed. Cir. 1995). More is needed. In the present case, the Office has not even reached the threshold addressed by *Duel.* That is, it has not cited any protein or nucleic sequence of any S-Nmase in its formulation of the obviousness rejection.

On pg. 9 of the Office Action, the PTO has alleged that "a search of the amino acid sequence databases against the amino acid sequence SEQ ID NO. 2 reveals that it matches 100% with the amino acid sequence derived from the same enzyme that was purified by Chatterjee". That observation is not germane to this case. The match identified by the Examiner refers to a 1999 publication (Chatterjee et al. JBC 274: 37407). Since the 1999 publication date of the reference is well after the 1996 priority date of the instant case, it is not prior art. It cannot be used to formulate or substantiate the instant rejection.

On pgs. 9-10, the Office has taken the position that *Duel* and *Bell* are not applicable to the instant application on grounds that Applicant is "not claiming DNA or a method based on a DNA sequence". Action at pg. 10. Respectfully, that strained reading of the case law misses the point. The PTO alleged that it would be obvious to make a (recombinant) cDNA encoding the enzyme from Chatterjee's isolation of the urine enzyme and Ausubel's textbook cloning methods. The PTO formulated the rejection without reference to any protein or nucleic acid sequence whatsoever, thereby making the Court's holding in *Duel* and *Bell* particularly relevent. The recombinant enzyme used in Applicant's claimed invention is not obvious nor can the method of using it be obvious in view of the limited disclosure cited by the PTO.

Respectfully, the Office has failed in its burden to make a *prima facie* case for obviousness. Reconsideration and withdrawal of rejection are requested.

The English translation of Ogita (of record) reports a bacterial sphinogmyelinase inhibitor called "F-10463a" that was isolated from withered grass stem fungus. Other inhibitors were not isolated and the assay provided (rat brain test) was limited to analysis of the F-10463a compound. Accordingly, it does nothing to remedy the defects already apparent in the present §103 rejection. It does not teach or suggested the claimed invention when taken alone or together with the other cited references.

Additionally, there is understanding in the field that bacterial and human sphinogmyelinases are different. There is no teaching or suggestion in Ogita that the F-10463a inhibitor would work against a human enzyme. The other cited references do not remedy this defect.

Applicant's prior response outlined significant advantages for using the claimed invention eg,, avoiding use of potentially hazardous human urine samples and obtaining sufficient amounts of enzyme to perform the method.

In marked contrast, the claimed invention avoids these and other drawbacks by providing, for the first time, a recombinant human neutral sphingomyelinase for use in the claimed methods. Thus, for example, the claimed invention solves prior problems of working with urine. A more reliable enzyme source can now be provided for use with the method.

Moreover, Applicant's disclosure provides for use of recombinant enzyme fragments and derivatives. Such portions of the human enzyme would be difficult, if not impossible to obtain from the native enzyme cited in the Office Action.

None of these significant advantages provided by Applicant's invention are taught or suggested by the cited references.

In view thereof, reconsideration and withdrawal of the rejection are requested.

Early consideration and allowance of the application are earnestly solicited.

If for any reason a fee is required, a fee paid is inadequate or credit is owed for any excess fee paid, you are hereby authorized and requested to charge Deposit Account No. **04-1105**.

Attached to this submission is a marked-up version of the changes made to the specification and claims. The attached page is captioned "version with markings to show changes made".

Respectfully submitted,

Date: 5 September 02

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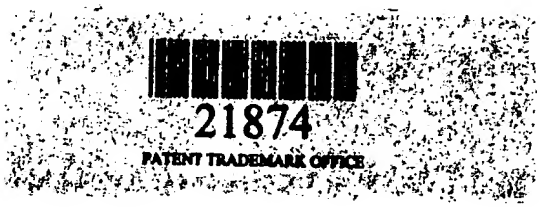

VERSION WITH MARKINGS TO SHOW CHANGES MADE

IN THE CLAIMS:

Claim 13 has been amended as follows:

13. (Amended) A method of identifying a compound useful in the diagnosis or treatment of a human neutral sphingomyelinase related disorder, comprising contacting a candidate pharmacological agent with a recombinant human neutral sphingomyelinase having an amino acid sequence represented by SEQ ID NO. 2 or fragment or derivative thereof and analyzing the mixture of the candidate agent and human neutral sphingomyelinase or fragment or derivative thereof, wherein the analyzing step further comprises comparing enzyme activity in the presence and absence of the agent, wherein the fragment or derivative of the human neutral sphingomyelinase has at least about 50% of the activity of the protein of SEQ ID NO.2.

The following new claim 31 has been added.

31. (New) The method of claim 13, wherein the fragment or derivative of the recombinant human neutral sphingomyelinase is at least about 70% identical to the protein of SEQ ID NO. 2

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